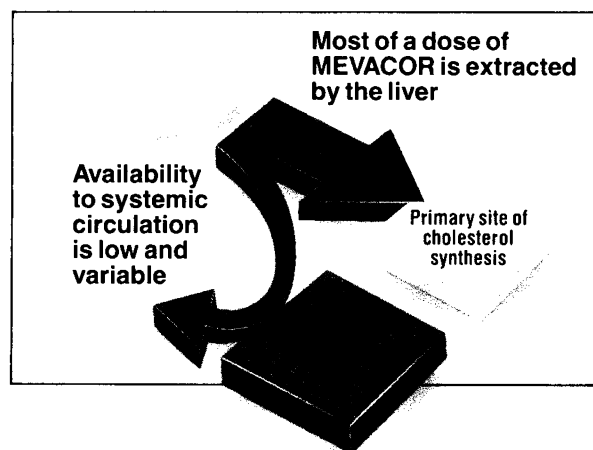


**MEVACOR works where it should:
at the primary site of cholesterol synthesis**

HIGHLY SELECTIVE

MEVACOR is the first agent to selectively inhibit cholesterol production at the primary site of synthesis. This selective activity means MEVACOR is highly effective—with only a low and variable amount of active drug available for systemic circulation.



MEVACOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

In clinical studies, marked persistent increases (to more than three times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year. It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy, and periodically thereafter in all patients.

For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and slit-lamp monitoring, please refer to the Prescribing Information.

For a Brief Summary of Prescribing Information, please see the back of this advertisement.

For many patients with primary hypercholesterolemia (Types IIa and IIb), when diet and other nondrug therapies are inadequate

MEVACOR[®]
(LOVASTATIN | MSD)

TABLETS, 20 mg 40 mg

MEVACOR[®]

(LOVASTATIN MSD)

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases.

Pregnancy and lactation.

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR[®] (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR[®] may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: Liver Dysfunction: Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 9% of adult patients who received lovastatin for at least one year in clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed areas of focal hepatitis. In this patient, transaminase levels returned to normal following discontinuation of therapy. Some of these patients had abnormal liver function tests prior to lovastatin therapy and/or consumed substantial quantities of alcohol.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy with lovastatin, and periodically thereafter in all patients. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR[®] (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR[®], were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: Several cases of rhabdomyolysis have been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥ 1 g/day) of nicotinic acid. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness, or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy, the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: General: Before instituting therapy with MEVACOR[®] (Lovastatin, MSD), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Lovastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Eye: There was a high prevalence of baseline lenticular opacities in the patient population included in the clinical trials with lovastatin. During these trials the appearance of new opacities was noted. The causal relationship of lovastatin to these findings has not been established.

Of 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase. There was no clinically significant change in visual acuity in the patients who had new opacities reported, nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity. Nevertheless, until further experience is obtained, it is recommended that patients placed on lovastatin therapy be examined with a slit lamp before or shortly after initiation of treatment and annually thereafter.

Homozygous Familial Hypercholesterolemia: MEVACOR[®] is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR[®] appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Drug Interactions: Immunosuppressive Drugs: Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin. See WARNINGS, Skeletal Muscle.

Coumarin Anticoagulants: In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prothrombin time, lovastatin in dosages up to 40 mg b.i.d. did not produce any consistent alteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin time can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenicity study in mice, a statistically significant ($p < 0.05$) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (12.5 and 62.5 times the maximum recommended human dose).

A statistically significant increase ($p < 0.05$) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose); no similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (12.5 or 62.5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known.

In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (6.25 and 312 times the maximum recommended human dose); no increase was seen at a dosage of 20 mg/kg/day (12.5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa. Importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region; acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and anorectal junction of the mouse and rat; however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose) or in a study of 24 months in the rat given 180 mg/kg/day (112 times the maximum recommended human dose).

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinomas in males (unadjusted $p < 0.025$). However, because the incidence of hepatocellular carcinomas observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are unclear.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

No drug-related effects on fertility were found in studies with rats.

Pregnancy: Pregnancy Category X. See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (highest tolerated dose—about 9 times the maximum recommended human dose). There are no data in pregnant women.

Nursing Mothers: Studies in rats have shown that lovastatin is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR[®], women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no

studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR[®] (Lovastatin, MSD) is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies due to adverse experiences attributable to MEVACOR[®]. About 2% of patients were discontinued from all studies (controlled and uncontrolled) due to adverse experiences attributable to MEVACOR[®], about one-third of these patients were discontinued due to increases in serum transaminases.

Clinical Adverse Experiences: Adverse experiences reported in patients treated with MEVACOR[®] are listed below and are shown in the table below.

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Gastrointestinal	4.9	—	34.1	2.1
Constipation	3.5	4.9	8.0	10.3
Dyspepsia	3.9	—	13.6	3.1
Flatulence	6.4	2.4	21.6	2.1
Abdominal pain cramps	5.7	2.4	5.7	5.2
Heartburn	1.6	—	9.0	—
Nausea	7.0	8.7	8.1	6.2
Musculoskeletal	—	—	—	—
Myalgia	1.1	—	1.1	—
Nervous System	2.0	1.2	—	1.0
Blurred vision	9.3	9.9	4.5	8.2
Skin	—	—	—	—
Rash pruritus	—	—	4.5	—
Special Senses	—	—	—	—
Blurred vision	1.5	—	1.1	3.1
Dysgeusia	0.8	—	1.1	—

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9% and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, Skeletal Muscle).

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to the concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, Skeletal Muscle).

Uncontrolled Clinical Studies: The adverse experiences observed in uncontrolled studies were similar to those seen in controlled clinical studies. Abnormal liver function tests were observed at a higher incidence than in the controlled studies (see WARNINGS, Liver Dysfunction). Myopathy (myalgia with marked CPK elevations) was reported in approximately 0.5% of patients (see WARNINGS, Skeletal Muscle).

Causal Relationship Unclear: Nervous System: Peripheral neuropathy has been reported; the relationship to lovastatin is uncertain. Visual evoked response, nerve conduction measurements, and electromyography in over 30 patients showed no evidence of neurotoxic effects of lovastatin.

Special Senses: Of 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase (see PRECAUTIONS).

Post-marketing Experience: Additional adverse experiences occurring since the drug was marketed are listed below.

Clinical Adverse Experiences:

Gastrointestinal: Hepatitis, cholestatic jaundice, anorexia, vomiting.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, flushing, malaise, and dyspnea.

Nervous System Psychiatric: Psychic disturbances, including anxiety, paresthesia.

Skin: Erythema multiforme, including Stevens-Johnson syndrome, toxic epidermal necrolysis.

Causal Relationship Unknown

Gastrointestinal: Pancreatitis, stomatitis.

Skin: Alopecia.

Nervous System Psychiatric: Depression, insomnia.

Metabolic: Edema.

Clinical Laboratory Test Findings

Liver Function Tests: Liver function test abnormalities, including elevated alkaline phosphatase and bilirubin.

Thyroid Function Tests: Rare reports of thyroid function test abnormalities in patients taking concomitant thyroxine.

OVERDOSAGE: The oral LD₅₀ of MEVACOR[®] in mice is 20 g/kg.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR[®] can be recommended. The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR[®] and should continue on this diet during treatment with MEVACOR[®]. MEVACOR[®] should be given with meals. The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, Clinical Studies for dose response results).

For those patients with severely elevated serum cholesterol levels (i.e., >300 mg/dL [7.8 mmol/L] on diet), MEVACOR[®] may be initiated at 40 mg/day.

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, Skeletal Muscle), the maximum recommended dosage is 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR[®] if cholesterol levels fall below the targeted range.

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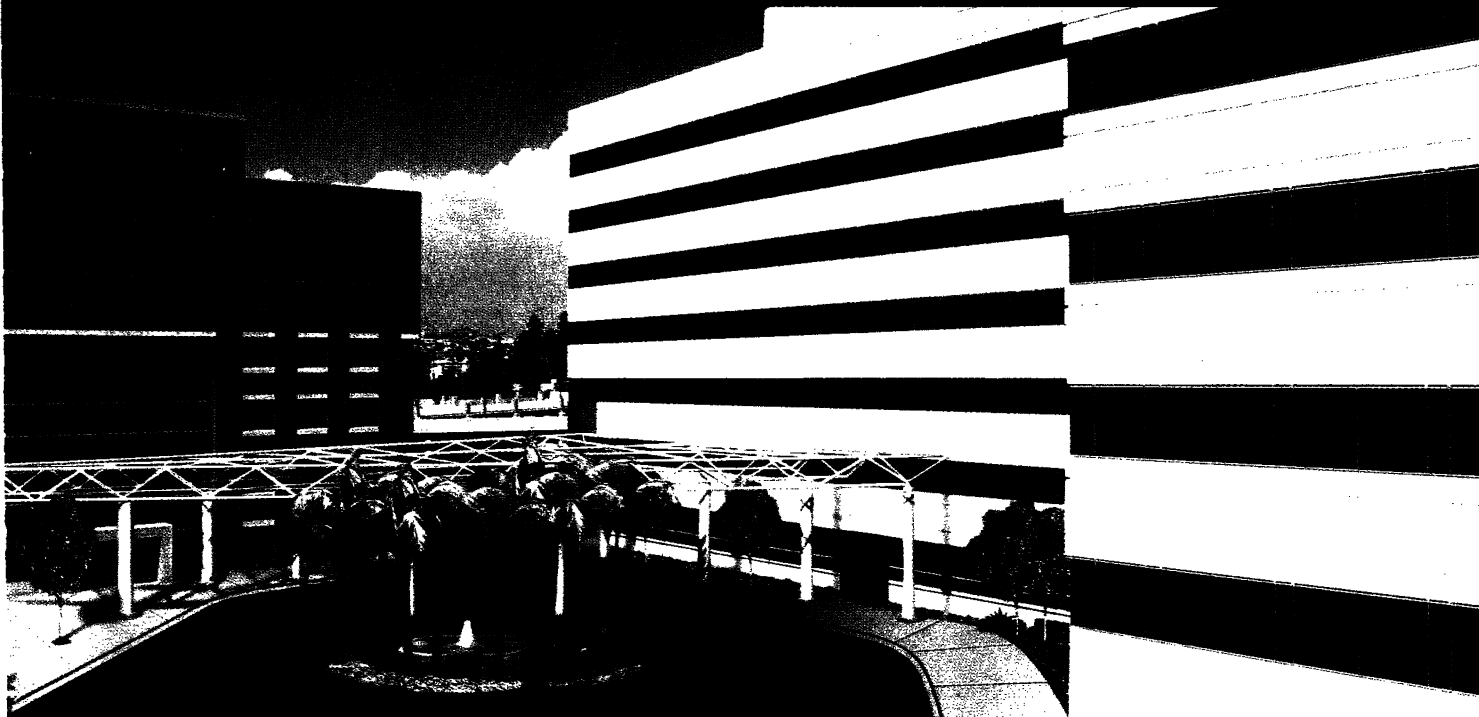
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**BuSpar relieves anxiety and returns
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... with no more sedation (10%) than induced by placebo (9%)¹
... without inducing significant cognitive² or functional impairment*
... without producing a benzodiazepine withdrawal syndrome³
upon discontinuation

Effective choice for anxiety

BuSpar[®]
Tablets, 5 mg and 10 mg
(buspirone HCl)

for a different kind of calm

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

For Brief Summary, please see following page.

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MJL8-4270

BuSpar® (buspirone HCl)

References: 1. Newton RE, et al. A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21. 2. Lucki I, et al. Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. 3. Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(SA):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: General—Interference with cognitive and motor performance: Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdrawal patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B. Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): Commonly Observed—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: Cardiovascular: tachycardia/palpitations 1%, CNS: Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%, EENT: Blurred vision 2%, Gastrointestinal: Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%, Musculoskeletal: Musculoskeletal aches/pains 1%, Neurological: Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%, Skin: Skin rash 1%, Miscellaneous: Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. Cardiovascular—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. Central Nervous System—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. EENT—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. Endocrine—rare: galactorrhea, thyroid abnormality. Gastrointestinal—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. Genitourinary—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. Musculoskeletal—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. Neurological—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. Respiratory—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. Sexual Function—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. Skin—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. Clinical Laboratory—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. Miscellaneous—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccups.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: Controlled Substance Class—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: Signs and Symptoms—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

MJLB-4270

Mead Johnson
PHARMACEUTICALS

A Bristol-Myers Company
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YOCON® YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubiaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors. Its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

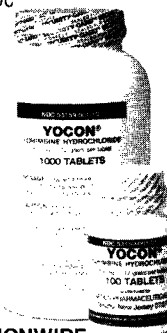
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188, McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85



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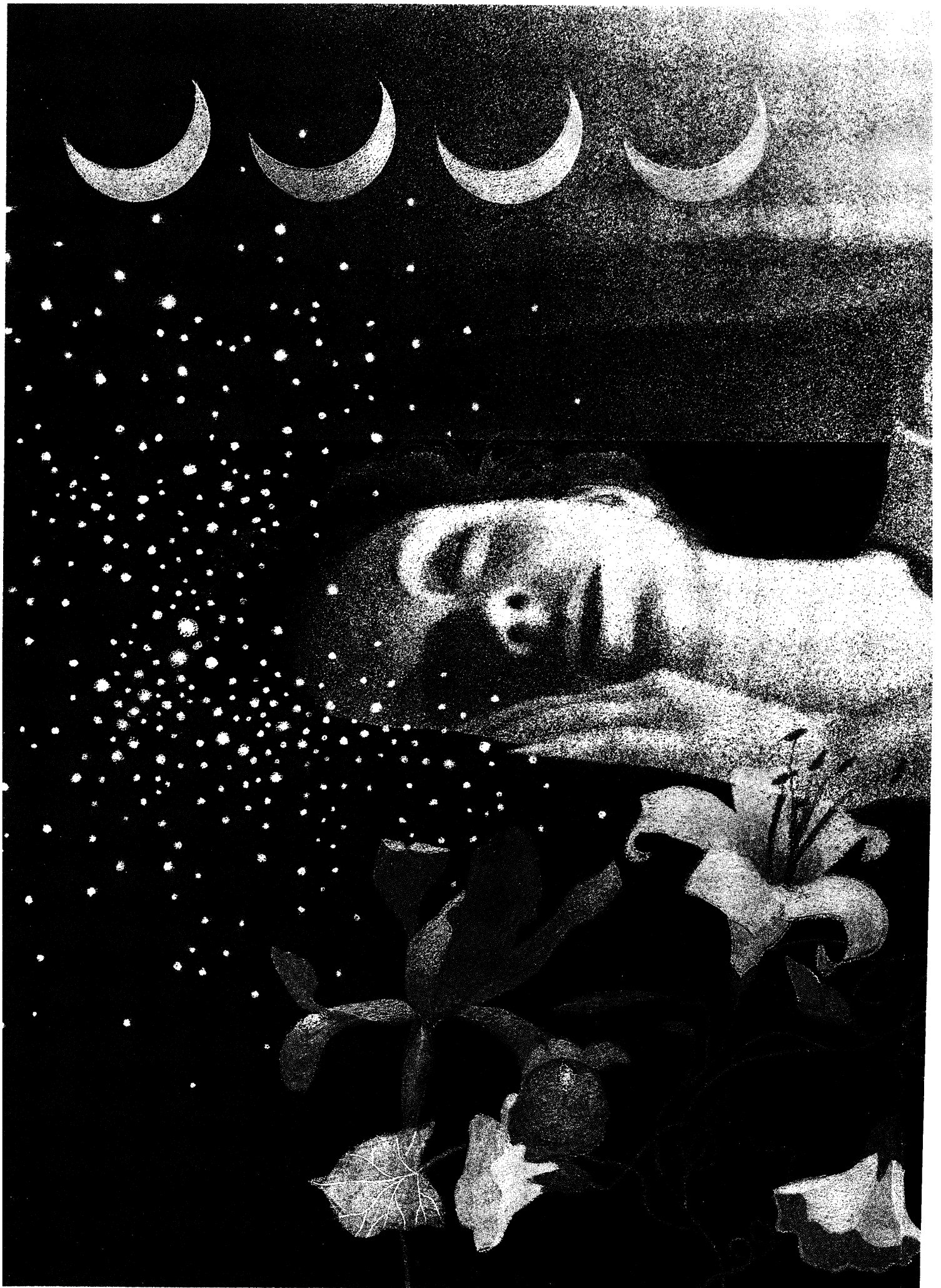
I.D. # 8500 G 1mg

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NEW

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estazolam ^{IV}

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The sleep of their dreams

A rapid, yet gentle onset

Clinical studies have demonstrated that ProSom initiates sleep within 15 to 30 minutes after bedtime.^{1,2}

Patients' responses in both short- and long-term sleep laboratory and outpatient efficacy studies indicated significant improvements in their ability to fall asleep.¹⁻³

A full night's duration

ProSom provides an average of 6 to 8 hours of improved sleep, with a significant reduction in nocturnal awakenings and wake time during sleep.¹⁻⁵ In fact, throughout multiple, independent efficacy studies, ProSom was shown to significantly improve *every* measure of sleep.¹⁻⁵

A clear return to morning

Daytime performance with ProSom was shown to be comparable to placebo-treated patients, with performance deficits, if any, shown to be short and transient.⁶ And clinical studies, including a 10-week efficacy trial, demonstrated no anterograde amnesia or short-term memory impairment.^{6,7}

NEW

 **ProSom**TM
estazolam®

When sleep doesn't come naturally



Please see brief summary of prescribing information on following page.




NEW

 **ProSom**[™]
estazolam ^{IV}

The sleep of
their dreams

- A rapid, yet gentle onset
- A full night's duration
- A clear return to morning

R_x

ProSom
2mg
Sig: 1 tablet h.s.
for sleep

References:

1. Lamphere J, Roehrs T, Zorick F, Koshorek G, Roth T. Chronic hypnotic efficacy of estazolam. *Drugs Exp Clin Res*. 1986;12(8):687-691.
2. Pierce MW, Shu VS. Efficacy of estazolam: The United States clinical experience. *Am J Med*. 1990;88(3A):6S-11S.
3. Walsh JK, Targum SD, Pegram V, et al. A multi-center clinical investigation of estazolam: short-term efficacy. *Curr Ther Res*. 1984;36(5):866-874.
4. Dominguez RA, Goldstein BJ, Jacobson AF, Steinbock RM. Comparative efficacy of estazolam, flurazepam, and placebo in outpatients with insomnia. *J Clin Psychiatry*. 1986;47(7):362-365.
5. Roehrs T, Zorick F, Lord N, Koshorek GL, Roth T. Dose-related effects of estazolam on sleep of patients with insomnia. *J Clin Psychopharmacol*. 1983;3(3):152-156.
6. Pierce MW, Shu VS, Groves LJ. Safety of estazolam: The United States clinical experience. *Am J Med*. 1990;88(3A):12S-17S.
7. Scharf MB, Mayleben DW, Fletcher KA, Shu VS, Pierce MW. Effect of single doses of estazolam and triazolam on memory function in adult insomniacs. Submitted for publication.

Brief Summary

CLINICAL PHARMACOLOGY:

The range of estimates for the elimination half-life varied from 10 to 24 hours. Benzodiazepine clearance is accelerated in smokers compared to nonsmokers, and there is evidence that this occurs with estazolam. This decrease in half-life, presumably due to enzyme induction by smoking, is consistent with other drugs with similar hepatic clearance characteristics. In all subjects the mean elimination half-life appears to be independent of the dose.

CONTRAINDICATIONS:

Contraindicated in pregnant women due to potential fetal damage. Women of childbearing age should be warned of the potential risk to the fetus.

WARNINGS:

Due to CNS-depressant effects patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and about possible combined effects with alcohol and other CNS-depressant drugs.

As with all benzodiazepines, amnesia, paradoxical reactions, and other adverse behavioral effects may occur. There have been reports of withdrawal symptoms of the type associated with CNS depressants following rapid decrease or abrupt discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE).

PRECAUTIONS:

General: Impaired motor and/or cognitive performance attributable to accumulation of benzodiazepines and active metabolites is a concern in certain patients (eg, those sensitive to benzodiazepines or those with a reduced capacity to metabolize and eliminate them) (see DOSAGE AND ADMINISTRATION). Elderly or debilitated patients and those with impaired renal or hepatic function should be advised to monitor themselves for signs of excessive sedation or impaired conditions.

May cause dose-related respiratory depression that is ordinarily not clinically relevant at recommended doses in patients with normal respiratory function. Monitor patients with compromised respiratory function appropriately.

Administered with caution to patients exhibiting symptoms of depression. Suicidal tendencies and intentional overdosage is more common in such patients.

Information for Patients: Inform patients about consumption of alcohol and other drugs; possible fetal damage and excretion in breast milk; hazards of operating machinery or driving; not increasing dose; and worsening of sleep after abrupt discontinuation.

Laboratory Tests: Not ordinarily required in healthy patients. When treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable.

Drug Interactions: Benzodiazepines may be potentiated by anticonvulsants, antihistamines, alcohol, barbiturates, monoamine oxidase inhibitors, narcotics, phenothiazines, psychotropic medications, or other drugs that produce CNS depression. Smokers have increased clearance of benzodiazepines (see CLINICAL PHARMACOLOGY).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies were conducted in mice and rats at doses of 0.8, 3, and 10 mg/kg/day and 0.5, 2, and 10 mg/kg/day, respectively. Evidence of tumorigenicity was not observed. Hyperplastic liver nodules were increased in female mice given mid- and high doses. The significance of such nodules in mice is not known. *In vitro* and *in vivo* mutagenicity tests did not show a mutagenic potential. Fertility in male and female rats was not affected by doses up to 30 times the usual recommended human dose.

Pregnancy: May cause fetal damage if administered during pregnancy. The child born of a mother taking benzodiazepines may be at risk for withdrawal symptoms and neonatal flaccidity during the postnatal period.

Labor and Delivery: No established use.

Nursing Mothers: Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness below the age of 18 not established.

Geriatric Use: Approximately 18% of patients studied were 60 years or older. The adverse event profile did not differ from that observed in younger individuals. Exercise care when prescribing to small or debilitated elderly patients (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS:

During clinical trials in which ProSom was administered to 1277 patients, the most commonly observed adverse events were somnolence, hypokinesia, dizziness, and abnormal coordination. The events listed below were also observed. Although these events occurred during treatment with ProSom, they were not necessarily caused by it.

Body as a Whole: abdominal pain, allergic reaction, asthenia, back pain, body pain, chest pain, chills, edema, fever, headache, jaw pain, lower extremity pain, malaise, neck pain, swollen breast, upper extremity pain.

Cardiovascular System: arrhythmia, flushing, palpitation, syncope; **Digestive System:** constipation, decreased appetite, dry mouth, dyspepsia, enterocolitis, flatulence, gastritis, increased appetite, melena, mouth ulceration, nausea, vomiting; **Endocrine System:** thyroid nodule; **Hematologic and Lymphatic System:** leukopenia, purpura, swollen lymph nodes; **Metabolic/Nutritional Disorders:** increased SGOT, thirst, weight gain, weight loss.

Musculoskeletal System: arthralgia, arthritis, muscle spasm, myalgia, stiffness; **Nervous System:** agitation, amnesia, anxiety, apathy, ataxia, circumoral paresthesia, confusion, coordination abnormal, decreased libido, decreased reflexes, depression, dizziness, dream abnormal, emotional lability, euphoria, hallucinations, hangover, hostility, hypokinesia, nervousness, neuritis, nystagmus, paresthesia, seizure, sleep disorder, somnolence, stupor, thinking abnormal, tremor, twitch. Minor changes in EEG patterns, usually low-voltage fast activity, were observed during therapy or withdrawal and are of no known clinical significance.

Respiratory System: asthma, cold symptoms, cough, dyspnea, epistaxis, hyperventilation, laryngitis, pharyngitis, rhinitis, sinusitis; **Skin and Appendages:** acne, dry skin, pruritis, rash, sweating, urticaria; **Special Senses:** abnormal vision, decreased hearing, diplopia, ear pain, eye irritation, eye pain, eye swelling, perverse taste, photophobia, scotomata, tinnitus; **Urogenital System:** frequent urination, hematuria, menstrual cramps, nocturia, oliguria, penile discharge, urinary hesitancy, urinary incontinence, urinary urgency, vaginal discharge/itching; **Postintroduction Reports:** Voluntary reports from non-US postmarketing experience have included rare occurrences of photosensitivity and agranulocytosis. Due to the uncontrolled nature of these reports, a causal relationship has not been determined.

DRUG ABUSE AND DEPENDENCE:

Controlled Substance: Schedule IV. **Abuse and Dependence:** Withdrawal symptoms have occurred following abrupt discontinuation of benzodiazepines. Symptoms range from mild dysphoria and insomnia to abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. Patients with a history of seizures are at increased risk. Withdraw gradually in patients taking benzodiazepines for a prolonged period. Monitor addiction-prone patients closely.

DOSAGE AND ADMINISTRATION:

Initial dose for adult and healthy elderly patients is 1-2 mg at bedtime. Increase dose carefully in the elderly. Consider an initial dose of 0.5 mg in small or debilitated older patients.

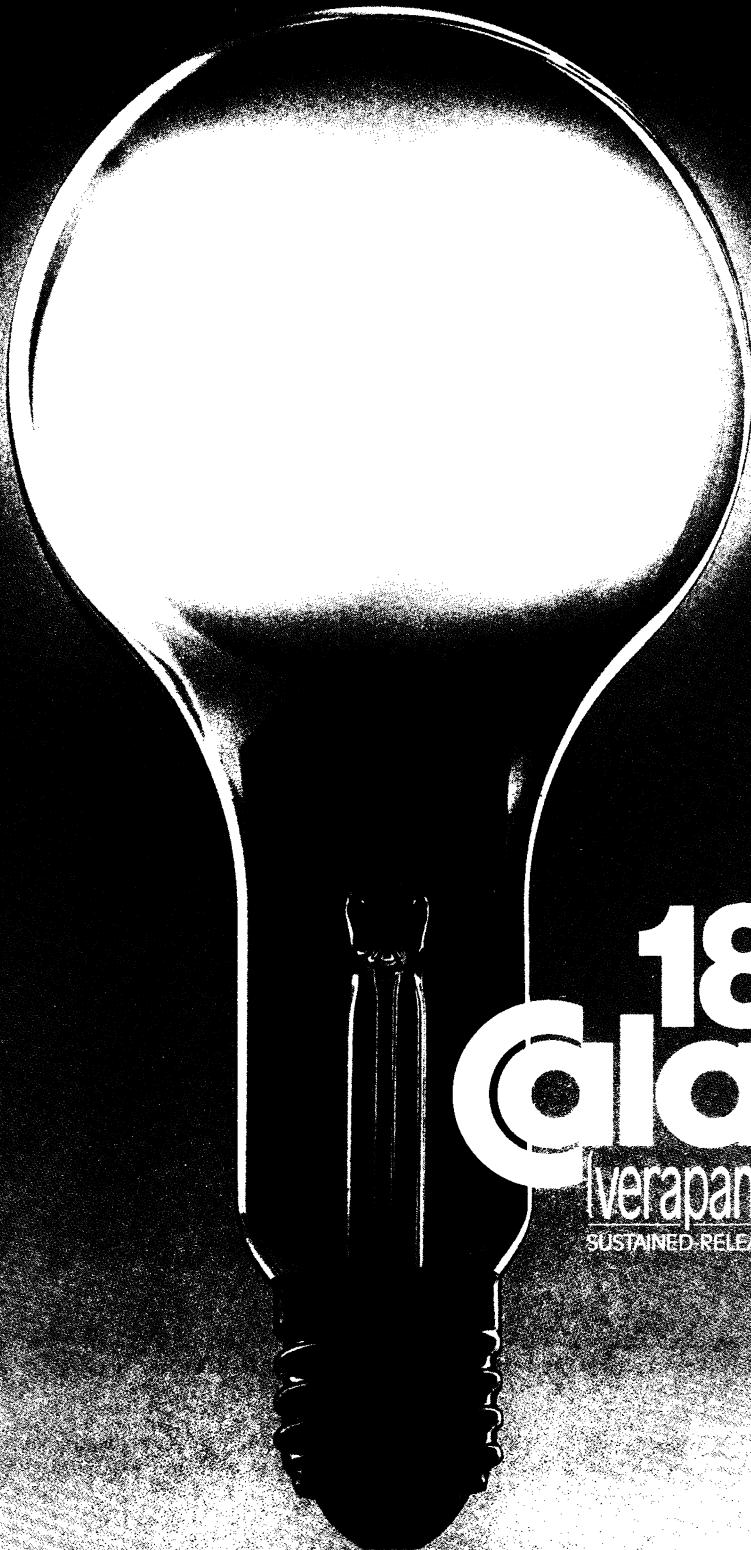
HOW SUPPLIED:

Available in 1 mg and 2 mg scored tablets.

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Revised: January, 1991

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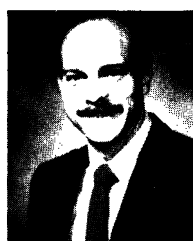
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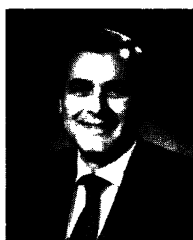
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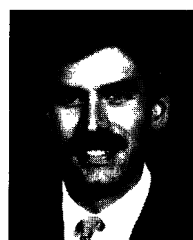
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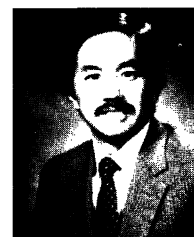
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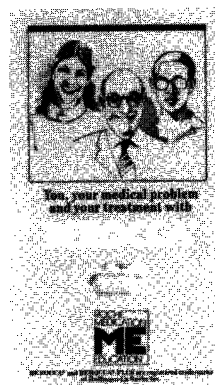


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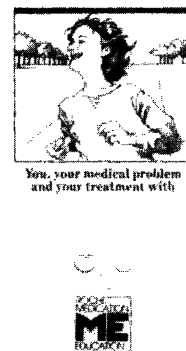
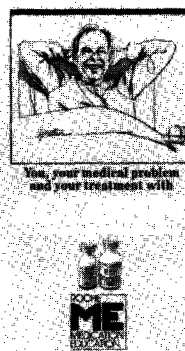
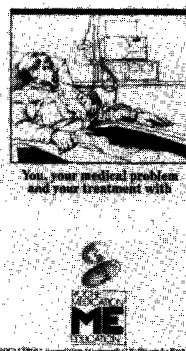
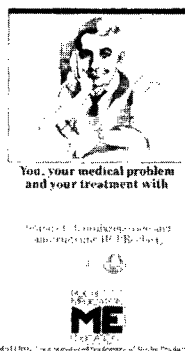
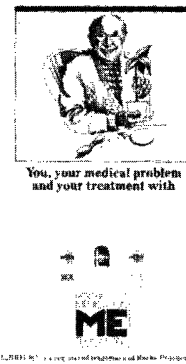
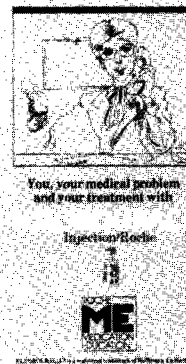
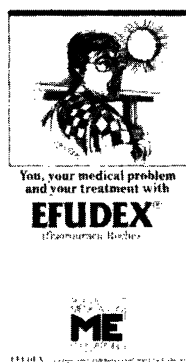
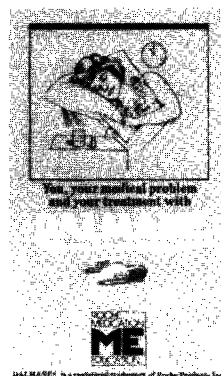


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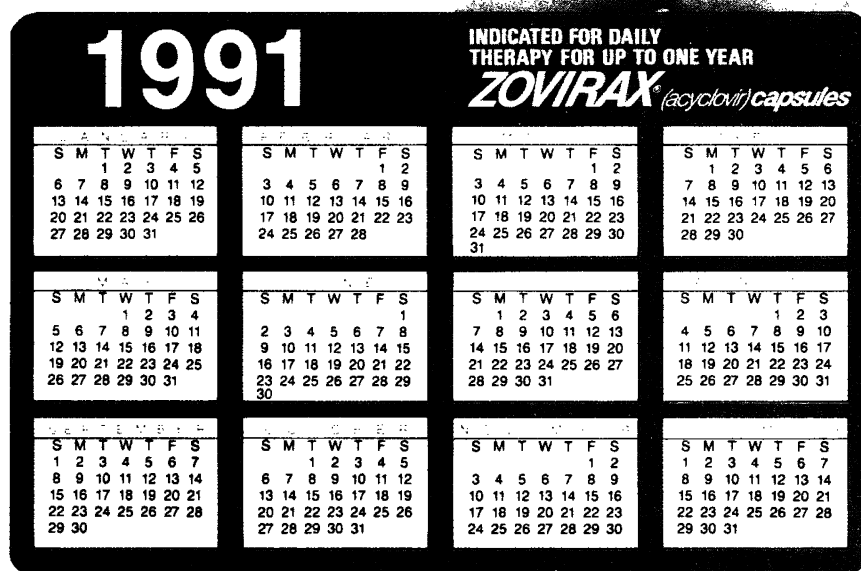
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ANNOUNCING A GREAT YEAR AHEAD FOR HERPES PATIENTS



1-YEAR INDICATION FOR DAILY THERAPY

Herpes patients can look forward to a great year ahead. Results of a recent clinical study show a lesion-free year for nearly half the patients treated with ZOVIRAX Capsules 400 mg b.i.d.*[†] For all ZOVIRAX Capsule recipients, recurrences during the study year were limited to a mean of 1.8, compared with a mean of 11.4 for placebo recipients.¹

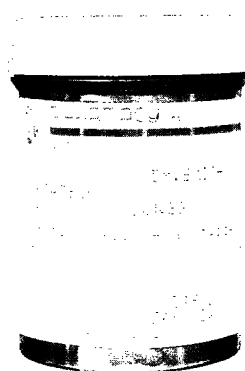
Daily use was also shown to be well tolerated. And this extended clinical study demonstrated no evidence of cumulative toxicity and no change in acyclovir sensitivity.^{1,2}

Prescribe daily ZOVIRAX Capsule therapy...and help keep your patients lesion-free longer.[†]

* Alternate maintenance regimens range from 200 mg t.i.d. to 200 mg five times daily.

[†] In a controlled study of 3 years' duration, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively.³

Please see brief summary of prescribing information on adjacent page.



ZOVIRAX[®]
(acyclovir) capsules

KEEPS HERPES PATIENTS LESION-FREE LONGER[†]

ZOVIRAX® CAPSULES ZOVIRAX® SUSPENSION (ACYCLOVIR)

BRIEF SUMMARY

INDICATIONS AND USAGE: Zovirax Capsules and Suspension are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

Zovirax Capsules and Suspension are also indicated for the acute treatment of herpes zoster (shingles).

Genital Herpes Infections: The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus orally administered Zovirax is not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes):

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax.

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered Zovirax given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of 283 patients who received 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52% and 63% of patients remained free of recurrences in the first, second and third years, respectively. Serial analyses of the 3 month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy. Re-evaluation will usually require a trial of acyclovir to assess the need for reinstitution of suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year.

Chronic suppressive therapy is most appropriate when, in the judgment of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, orally administered Zovirax should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual re-evaluation.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

Herpes Zoster Infections: In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to Zovirax and 94 to placebo), Zovirax (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to Zovirax and 43 to placebo), Zovirax (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia or hyperesthesia).

CONTRAINDICATIONS: Zovirax Capsules and Suspension are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations.

WARNINGS: Zovirax Capsules and Suspension are intended for oral ingestion only.

PRECAUTIONS: General: Zovirax has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS—Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY—Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced. The clinical effects of this combination have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see Pharmacokinetics).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay.

Acyclovir was tested in two *in vitro* cell transformation assays. Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters, higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro*. In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in man. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels. Results in the other five mammalian cell loci follow: at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels. At a higher dose in the rat (50 mg/kg/day, s.c.), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels). In a rat pre- and postnatal study at 50 mg/kg/day s.c. (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F₂ generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy. Plasma levels were not measured in the one month study and were 24 to 48 times human levels in the six month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for one month (21 to 41 times human levels) and i.d. dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels).

Pregnancy: Teratogenic Effects: Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity. In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of Zovirax and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when Zovirax is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Herpes Simplex: Short-Term Administration: The most frequent adverse reactions reported during clinical trials of treatment of genital herpes with orally administered Zovirax were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%).

Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with orally administered Zovirax (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration: The most frequent adverse reactions reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 Zovirax-treated patients were: nausea (4.8%), diarrhea (2.4%), headache (1.9%) and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with Zovirax for 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%) and rash (1.5%). The most frequent adverse reactions reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were: headache (1.5%), rash (1.3%) and paresthesia (0.8%). Reactions reported by 329 patients during the third year include asthenia (1.2%), paresthesia (1.2%) and headache (0.9%).

Herpes Zoster: The most frequent adverse reactions reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral Zovirax 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%) and constipation (0.9%). The 323 placebo recipients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%) and constipation (2.4%).

OVERDOSAGE: Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days; rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. A 6 hr hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 10 days.

Chronic suppressive therapy for recurrent disease: 400 mg (two 200 mg capsules or two teaspoonfuls [10 mL] suspension) 2 times daily for up to 12 months, followed by re-evaluation. See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

Intermittent Therapy: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Acute Treatment of Herpes Zoster: 800 mg (four 200 mg capsules or four teaspoonfuls [20 mL] suspension) every 4 hours orally 5 times daily for 7 to 10 days.

Patients With Acute or Chronic Renal Impairment: Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment. Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications:

Normal Dosage Regimen (5x daily)	Creatinine Clearance (mL/min/1.73m ²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval (hrs)
200 mg every 4 hours	> 10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
800 mg every 4 hours	> 25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

For patients who require hemodialysis, the dosing schedule should be adjusted so that a dose is administered after each dialysis.

References: 1. Mertz GJ, Jones CC, Mills J, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection: a multicenter double-blind trial. *JAMA*. 1988;260:201-206. 2. Mertz GJ, Eron L, Kaufman R, et al. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. *Am J Med*. 1988;85(suppl 2A):14-19. 3. Data on file, Burroughs Wellcome Co., 1990.

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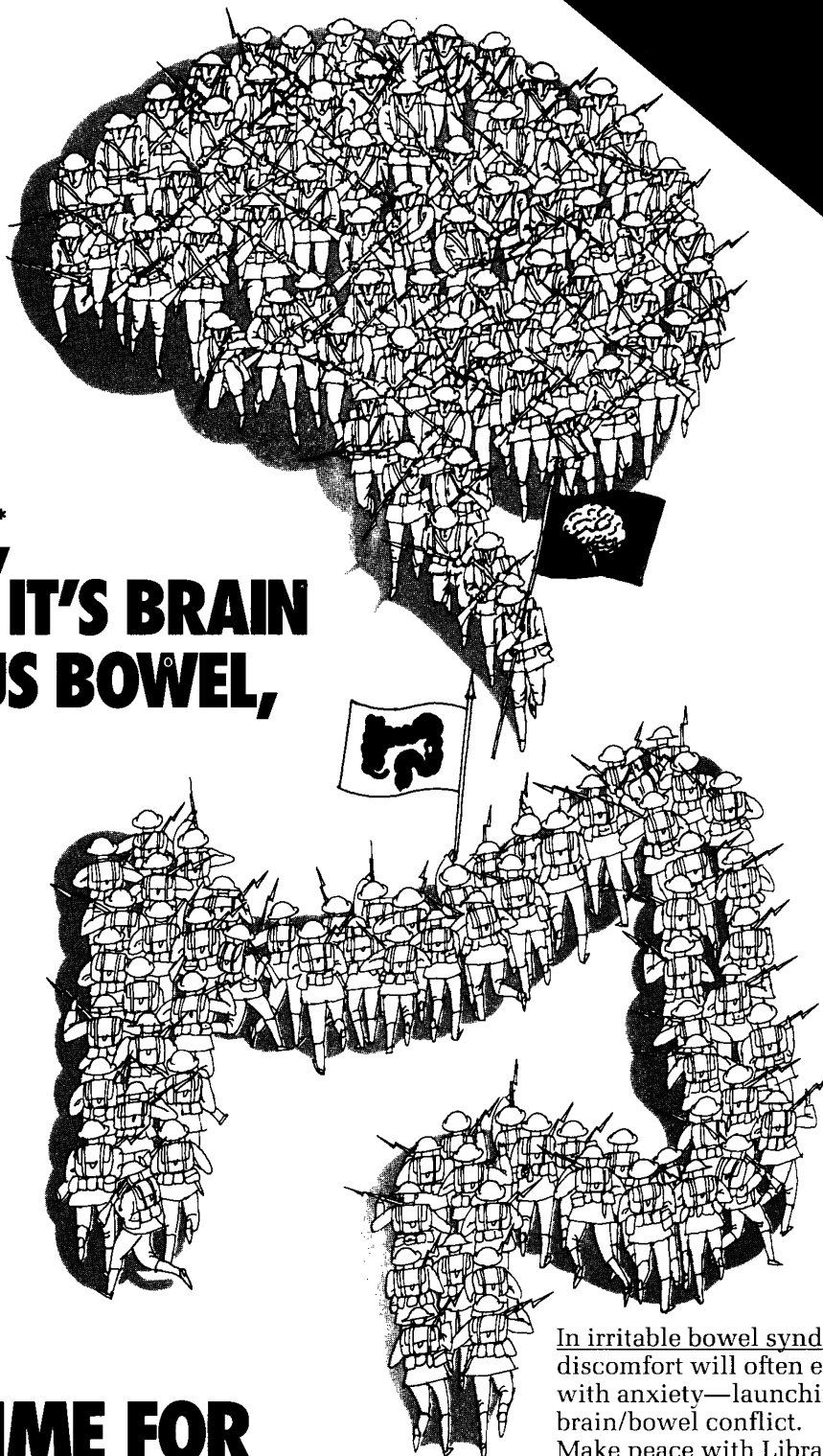
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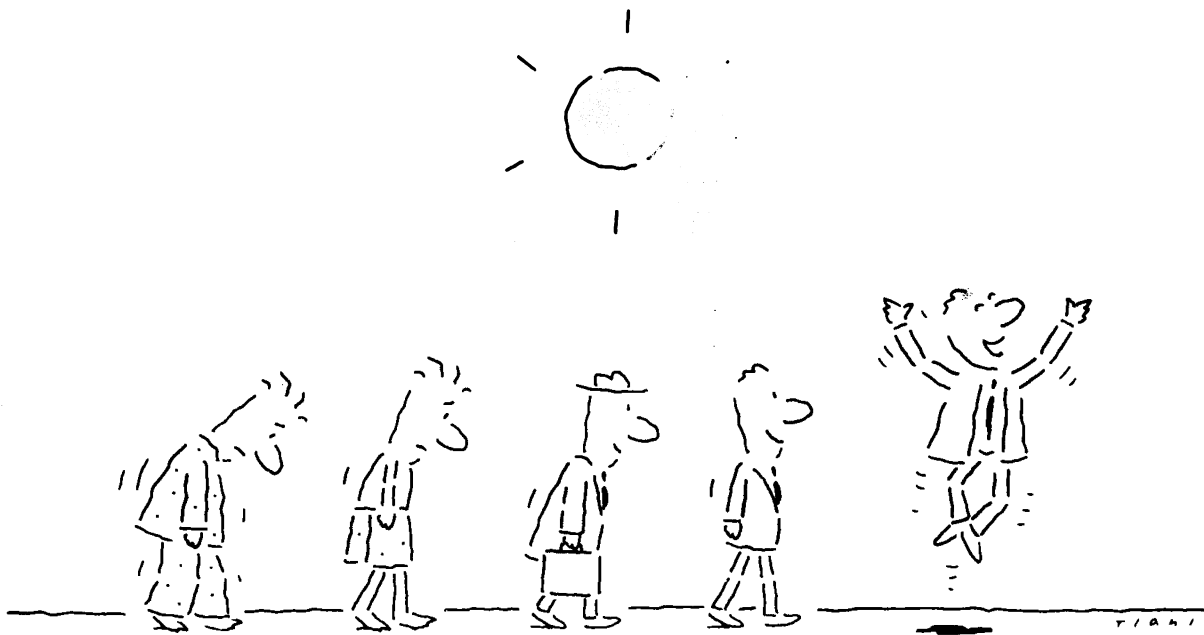
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(Continued from Page 474)

PHYSICIANS WANTED

RADIOLOGIST—SAN FRANCISCO BAY AREA. Growing outpatient imaging practice with CT/MRI. Salary leading to partnership. Send CV to Murray Solomon, MD, 450 Sutter St, Ste 835, San Francisco, CA 94108; (415) 296-8654.

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SEATTLE: BC/BE General Internist to join BC Internists' group with three Seattle area offices. No income guarantee; group and location excellent. Call or write Douglas Bovee, MD, 3203 W. McGraw, Seattle, WA 98199; (206) 285-3139.

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COLORADO. BC/BE INTERNIST to join three Internists in multispecialty group. Excellent opportunity for person interested in rural living, mountain recreation, and health care for medically underserved population. Send CV to Marguerite Salazar, 204 Carson Ave, Alamosa, CO 81101; (719) 589-5161.

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FAMILY PRACTICE PHYSICIANS. San Diego Area. BC/BE Family Practitioners for multispecialty group of 200-plus physician staff. Excellent fringe benefits, salary guarantee and incentive. Shareholder eligible after two years. Send CV with references to Office of the Medical Director, PO Box 129229, San Diego, CA 92112-9229.

CARSON CITY, NEVADA. Pediatrician wanted to join me in Primary Care practice. Part-time or full-time. Great family environment in Sierras 30 miles south of Reno. Contact Susan Pintar, MD, FAAP, 1001 N. Mountain, Ste 3M, Carson City, NV 89703; (702) 883-9003.

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(Continued on Page 476)

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PHYSICIANS WANTED

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PSYCHIATRY DIRECTOR—NORTHWEST. Regional Acute Care hospital seeking Director for new 20-bed inpatient Psychiatry unit. Previous experience desirable in program development and inpatient administration. Ideal candidate traits include team player, good communicator, and leadership. Opportunity for outpatient practice. Community known for quality of life, outdoor recreation and progressive health care. First year income guarantee, interview and relocation expenses, plus on-going Director stipend. Contact Alex Johnson, 1 (800) 327-1585.

FAMILY PRACTICE OPPORTUNITIES AVAILABLE IN Nevada, Washington, Texas, Louisiana, and Florida. For details, call Eloise Gusman; 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

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INTERNIST BC/BE. Current associate leaving for academic position. Busy Internal Medicine practice available July 1991. Currently netting \$155K, on call every seventh weekend. If you desire to enjoy life while maintaining a fully established and challenging practice send CV to Cecil Bullard, MD, 5339 N. Fresno, #107D, Fresno, CA 93710.

EMERGENCY MEDICINE. Emergency Medicine group seeking career oriented ACLS, ATLS certified physician for an immediate opening. Moderate volume; income \$140,000 plus. Great outdoor activities including hunting, fishing, boating, skiing, sailing, camping, and hiking in south central Washington on the Columbia River. Send CV to Kennewick Emergency Physicians, PS, PO Box 6192, Kennewick, WA 99336-6192; or call (509) 627-1798.

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SEATTLE, Washington suburban 26 physician primary care group has immediate need for Family Physicians and Internists. Area growth has created the need for a team physician who enjoys work as well as play in the beautiful (and affordable) Pacific northwest. Remuneration includes salary, bonus, and fringe benefit package. For more information, please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

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PEDIATRICIAN. Well established busy solo-practice available in suburban Seattle area. Excellent location adjacent to modern hospital. Level II newborn nursery. Ideally suited for Pediatrician with some experience who likes independence. Building may be purchased at later date. Present Pediatrician to retire this fall. Will introduce. Inquiries to Evergreen Pediatrics, 12819 120th Ave NE, Kirkland, WA 98034.

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MULTISPECIALTY MEDICAL CLINIC seeking Family Practice or Emergency Room Physician for their fast-paced Urgent Care department. 13 to 15 six-hour shifts per month with expansion of hours with the completion of a satellite facility. Board certified. Partnership track. Contact Jeanette Applegate at the Santa Cruz Medical Clinic, 2025 Soquel Ave, Santa Cruz, CA 95062; (408) 458-5592.

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CARDIOLOGY. Invasive Cardiologist join noninvasive; new Cath lab; north bay area. Huge opportunity. Electrophysiologist even better. Résumé to Number 234, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602. ASAP.

ESTHETIC SURGERY—SOUTHERN CALIFORNIA. BC General Plastic Surgeon to associate with ENT. Practice 99% cosmetic. Desire emphasis in breast/body contouring to complement current practice. Send CV to PO Box 3421, Santa Barbara, CA 93120.

BC/BE PULMONARY/CRITICAL CARE—SAN FRANCISCO BAY AREA. Physician sought to join two busy Pulmonologists in Marin county, 10 miles north of San Francisco. Excellent opportunity to be part of a well established practice, which would include inpatient and outpatient consultation and active involvement in the Intensive and Coronary Units at a superb community hospital. Guaranteed salary and benefits are available now but we will be willing to wait for completion of training in 1991. Send CV to Alan Margolin, MD, 900 S. Eliseo Dr, Greenbrae, CA 94904.

SPOKANE, WASHINGTON. Primary Care Physicians join with Annashae Corporation in providing patient care to the families of the men and women serving in the Armed Forces. Immediate Emergency Room positions available in Spokane, Washington. Weekends and holidays. Competitive remuneration. Malpractice covered. Licensure any state. ACLS required. Contact in confidence Annashae Corporation, 230 Alpha Park, Cleveland, OH 44143-2202; 1 (800) 245-2662, EEC/MF.

PATHOLOGIST, BC/BE—CENTRAL CALIFORNIA VALLEY. Seven member group seeks associate for independent multiple hospital and private laboratory practice. Send CV to Robert F. Chard, MD, Delta Pathology Associates Medical Group, 2291 W. March Ln, Ste 179E, Stockton, CA 95207.

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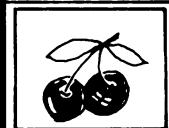
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PHYSICIANS WANTED

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

JUNIOR FACULTY INTERNIST. University of California, San Francisco, Valley Medical Center, Fresno Medical Education Program, Department of Family Practice seeks recent BE Internal Medicine graduate to attend on a general Internal Medicine ward, teach in the ambulatory setting and contribute to the intellectual life of the Department. Our full-time experienced Senior Internist will provide faculty development, consultation, and backup. VMC is a major affiliate of UCSF School of Medicine sponsoring several well regarded programs, including Internal Medicine. Delightful and affordable central California location. Salary guarantee and faculty practice plan incentive. Available July 1, 1991. Send CV to Robert Heiligman, MD, Assistant Chief of Family Practice, 2212 N. Winery, #130, Fresno, CA 93703. EOE, women and minorities are encouraged to apply.

INTERNAL MEDICINE PHYSICIAN (BC/BE) sought to join distinguished group of five others in a highly respected and successful practice situation in large east San Francisco bay city. The group owns its own modern building located in the heart of the medical community and within walking distance of two excellent hospitals. Excellent financial arrangements and benefits. Clinical faculty appointment with UCSF possible. For full details contact Mr Clifford Carpenter, (415) 834-7559, fax (415) 451-5517. CVs to 245 Lee St, Ste 109, Oakland, CA 94610.

MEDICAL DIRECTOR: HIV Clinic of Marin County, California. Full-time position approximately June, 1991 for MD with interest and experience in HIV Primary Care. Salary commensurate with experience, plus benefits. BC/BE, Family Practice, Internal Medicine. Send CV/résumé to Louise Fuller, AIDS Program, Department of Health and Human Services, 18 Professional Center Parkway, San Rafael, CA 94904; for information: (415) 499-6722.

FAMILY PRACTICE RESIDENCY FACULTY POSITION—CASPER, WYOMING. University of Wyoming Family Practice Residency-Casper is seeking an experienced, clinically oriented, BC Pediatrician to be the Pediatric Coordinator of an 8-8 Family Practice residency program. Level II Nursery skills are a must. 60% teaching, 20% direct patient care, 20% research. This is a tenure track position. University approval will be required prior to filling this position. Come join us in beautiful Wyoming. The University of Wyoming is an affirmative action/EOE. Contact Dr David Driggers, Director, University of Wyoming Family Practice Residency, 1522 E. "A" St, Casper, WY 82601; (307) 266-3076.

SOUTHERN CALIFORNIA—CLINICAL ALLERGISTS/IMMUNOLOGISTS AND PEDIATRIC PULMONOLOGIST

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Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, Walnut Center, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

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DENVER, COLORADO – A young, boarded Pediatrician practicing near our 200-bed hospital in the Denver suburbs for the past two years is now seeking an associate.

LAYTON, UTAH – A multi-speciality group here is seeking to add their third Pediatrician. Also, a three-physician group, with two offices, is in need of another member. Layton is 20 miles north of Salt Lake City and 15 miles south of Ogden.

For more information send CV to: Gordon Crawford, Manager, Professional Relations, Humana Inc., Dept. HH-4, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

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OB/GYN—SOUTHERN CALIFORNIA. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

PEDIATRICIANS—SOUTHERN CALIFORNIA. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

IMMEDIATE OPENING. BC, recently eligible, Internal Medicine. Assume substantial practice in three person group adjacent to Tri-City Hospital, Oceanside, California. Call (619) 724-8683.

EMERGENCY MEDICINE UNIVERSITY POSITION. The University of California, Davis, School of Medicine, is recruiting for a full-time faculty. The position will be at the Assistant or Associate Professor level. The Division of Emergency Medicine and Clinical Toxicology is undergoing rapid academic development and has an approved residency program in Emergency Medicine. The UCDMC Emergency Department provides comprehensive emergency service and is a major trauma center in northern California. The Department is a Paramedic Base Station and Training Center, and in addition, has an active Helicopter Service and Regional Poison Center. Candidates must be BC/BE in Emergency Medicine and be eligible for licensure in California. A letter outlining teaching background, interests, experience, and research in addition to a CV and the names of five references should be sent to Robert W. Derlet, MD, Chair, Emergency Medicine Search Committee, Tr 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817. Applications will not be accepted after April 30, 1991. The University of California is an Affirmative Action/Equal Opportunity Employer.

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— FRINGE BENEFITS —

(Continued on Page 479)

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PHYSICIANS WANTED**SAN FRANCISCO BAY AREA
BC/BE INTERNISTS**

We are currently seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 pre-paid health plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city, and the extensive cultural and recreational activities of northern California. As part of our large, multi-specialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to:

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FULL TIME MD POSITION AT THE LEVEL OF ASSISTANT/ASSOCIATE PROFESSOR OF CLINICAL FAMILY PRACTICE available in the Department of Family Practice, University of California, Davis. Must be BC by the American Board of Family Practice with interest, training, and/or experience in administration, teaching, research, academic publication, and Obstetric activities. The position will remain open until May 31, 1991. Send CV with list of three to five references to Robert C. Davidson, MD, Department of Family Practice, University of California, Davis, 2221 Stockton Blvd, Sacramento, CA 95817. The University of California is an affirmative action, equal opportunity employer.

PEDIATRICIAN—Salt Lake City area. Progressive community, excellent cultural and recreational opportunities. Thriving multispecialty practice or solo practice location. Top remuneration. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

OB/GYN—Salt Lake City area. Progressive community, excellent cultural and recreational activities. Thriving independent practice in multispecialty group location with excellent coverage. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

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PRACTICE OPPORTUNITIES. Family Practice, Internal Medicine, and Obstetrics and Gynecology positions available in San Diego, California, Phoenix, Arizona, Seattle, Washington, and Salt Lake City, Utah. Contact Eric Bennett, PO Box 5316, Scottsdale, AZ 85261; (602) 998-4540.

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FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

INTERNIST—Salt Lake City area. Progressive community, excellent skiing, hiking, as well as close proximity to major city. Independent or multispecialty group locations. Outstanding remuneration package. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

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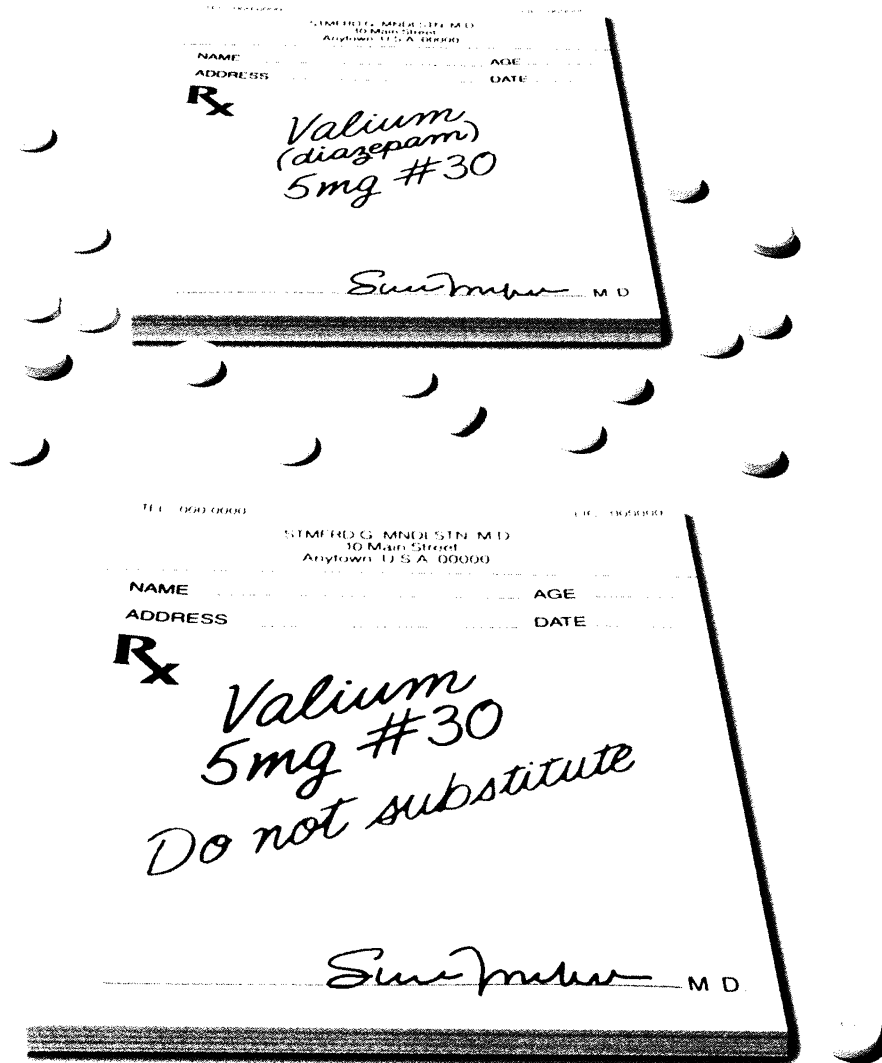
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